

# Parenteral Fish Oil Monotherapy in the Management of Patients With Parenteral Nutrition–Associated Liver Disease

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**Objectives:** To update knowledge on the management of parenteral nutrition–associated liver disease (PNALD) and to review the clinical data on the use of parenteral fish oil for reversal of PNALD.

**Data Sources:** A literature review was conducted by searching the MEDLINE database (May 1, 2009) using the keywords *parenteral nutrition–associated liver disease, fish oil, omega-3, Omegaven, and lipid emulsion.*

**Study Selection:** All articles reporting clinical cases with the use of parenteral fish oil for management of PNALD.

**Data Extraction:** Three reviewers independently analyzed the epidemiological, clinical, and treatment data of the articles.

**Data Synthesis:** Six case reports (10 patients) and 2 cohort studies (12 and 18 patients) were analyzed.

**Conclusions:** Fish oil–derived emulsions have been demonstrated to reverse preexisting PNALD and to prevent and treat essential fatty acid deficiency. Its ability to prevent PNALD is currently under investigation. Although the mechanism has yet to be fully understood, the advantages of fish oil–based lipid emulsions over soybean oil–based lipid emulsions seen to date suggest that fish oil–based emulsions would be better suited for use in long-term parenteral nutrition.

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**T**HE INTRODUCTION OF PARENTERAL nutrition (PN) has improved the outcome of patients unable to absorb adequate enteral nutrients, usually secondary to insufficient intestinal length or function.<sup>1</sup> Although PN is life saving, prolonged use of PN has been associated with hepatobiliary dysfunction, commonly referred to as PN-associated liver disease (PNALD).<sup>2</sup> Parenteral nutrition–associated liver disease is more prevalent in the pediatric population and is a significant life-threatening complication. Patients diagnosed with PNALD have a mortality rate approaching 100% within a year of diagnosis if they are unable to be weaned off PN or fail to receive a liver and/or intestinal transplant.<sup>3</sup> The goal of treating PN-dependent patients is to increase enteral feeds so that PN may be discontinued. Management of patients with compromised intestinal integrity, however, is usually a competition between intestinal adaptation and onset of PNALD. Available preventive and treatment strategies for this disease are limited and have achieved moderate success at best.

Parenteral nutrition is typically administered in combination with a parenteral lipid emulsion to provide a source of non-protein calories and prevent essential fatty acid deficiency (EFAD). Mounting evidence indicates that PNALD may in part be due to the composition of the conventional soybean oil–based lipid emulsions. These lipid emulsions contain phytosterols and proinflammatory  $\omega$ -6 fatty acids, both of which have been shown to be associated with PNALD.<sup>4</sup> Recent reports describing an alternative, fish oil–based lipid emulsion have shown promising results in the treatment of PNALD.<sup>5-12</sup> The aim of this review is to describe the impact of parenteral fish oil in PN-dependent patients on the clinical management of patients with PNALD, with an emphasis on the rationale and outcomes of experimental use.

## HISTORICAL NOTES

Over the last century, advancements in surgical technique and postoperative care have allowed more patients to undergo increasingly complex operations. It is known that surgical morbidity and mortality greatly

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depend on preoperative and postoperative nutritional status.<sup>13</sup> Naturally, general surgeons frequently perform procedures that leave patients unable to take enteral feeds for varying amounts of time. This led surgeons to become more interested in the field of nutrition and ultimately resulted in the development of PN.<sup>1</sup> In 1968, Dudrick et al<sup>14</sup> described the first long-term administration of PN in a female neonate. Today, more than 30 000 patients depend on PN for survival. Although there are many complications associated with PN noted in the discussion that follows, PN has become a vital treatment modality and an integral part in managing surgical patients and premature infants.

Early in its development, PN was mainly composed of protein hydrolysates and dextrose. Its use was hindered by its inability to meet total energy requirements. Moreover, the lack of essential fatty acids prevented it from being used as a long-term treatment. This led to the investigation of the use of fat in PN. Early attempts to infuse fat intravenously in the 1920s were plagued with chemical and pharmacological incompatibilities. In 1961, the first lipid emulsion that proved suitable for parenteral use in humans was created.<sup>15</sup> This soybean oil-based lipid emulsion, Intralipid (Baxter Healthcare, Deerfield, Illinois), was considered safe because the side effects were minimal and no severe adverse outcomes had been observed.<sup>16</sup> Although Intralipid was already used clinically in Sweden in 1962, its adoption for use in the United States lagged behind until the 1970s. Today, only 2 lipid emulsions, Intralipid and Liposyn (Hospira Inc, Lake Forest, Illinois), are approved by the US Food and Drug Administration to be used in the United States, and they are both derived from soybean oil.

## EPIDEMIOLOGY OF PNALD

Parenteral nutrition-associated liver disease is a spectrum of PN-associated hepatobiliary disorders, ranging from simple steatosis to cholestasis, cholelithiasis, hepatic fibrosis, and ultimately progression to cirrhosis, portal hypertension, and end-stage liver disease.<sup>17</sup> Steatosis is the most common finding in adults, while intrahepatic cholestasis is most often found in neonates and infants. In these young patients, cholestasis occurs early and hepatic dysfunction can rapidly progress. The prevalence of PNALD varies considerably among studies, but it is estimated to be approximately 40% to 60% in infants and up to 85% in neonates who are receiving long-term PN for intestinal failure.<sup>17</sup> Approximately 15% of patients who receive long-term PN eventually develop end-stage liver disease, which often leads to combined intestinal and liver transplant.<sup>18</sup>

## ETIOLOGY OF PNALD

The mechanism for PNALD remains to be elucidated, but most investigators invoke a multifactorial theory. Established risk factors for the development of PNALD are prematurity, low birth weight, duration of PN, and number of septic episodes.<sup>17,19</sup> Macronutrient excess, whether parenteral protein, lipids, or general overfeeding, has been associated with the onset of PNALD as well as an underlying diagnosis of gastroschisis or jejunal atresia.<sup>19</sup>

The source of fat in parenteral lipid emulsions has been demonstrated to play a role in developing hepatobiliary complications.<sup>4</sup> Currently, the only US Food and Drug Administration-approved intravenous lipid emulsions are those derived from either soybean oils alone (Intralipid, Liposyn III) or a combination of soybean and safflower oils (Liposyn II). These vegetable oil-based lipid emulsions contain significant quantities of phytosterols, which have been shown to accumulate in patients' serum and result in cholelithiasis.<sup>4</sup> Moreover, long-term use of a soybean oil-based lipid emulsion leads to a progressive increase of phytosterol content in cell membranes and plasma lipoproteins, which has been associated with the onset of PNALD in children receiving long-term PN.<sup>20</sup>

These vegetable oil-based lipid emulsions also contain high amounts of  $\omega$ -6 polyunsaturated fatty acids, which act as substrates for the formation of lipid hydroperoxides. Increased production of free radicals resulting in oxidative damage may be linked to the onset of hepatobiliary complications and can be reduced by enhancing antioxidant capacities. The higher susceptibility to oxidation of  $\omega$ -6 polyunsaturated fatty acids necessitates enrichment with the antioxidant  $\alpha$ -tocopherol to counteract formation of reactive oxygen species, although current levels may not be sufficient.

Another crucial factor in the development of PNALD is inflammation.  $\omega$ -6 Polyunsaturated fatty acids have been shown to increase the production of inflammatory mediators. Increasing levels of  $\omega$ -6 polyunsaturated fatty acids by parenteral soybean oil-based lipid emulsions may initiate or worsen inflammatory states and have been shown to have immunosuppressive effects.<sup>21</sup> These factors together could account for the increased incidence of PNALD seen with the use of parenteral administration of soybean oils.

## CONVENTIONAL MANAGEMENT OF PNALD

The current management of PNALD is summarized elsewhere.<sup>22</sup> The ideal strategy is to decrease PN administration and gradually reintroduce enteral feeds. The use of trophic feedings confers additional benefit as it can restore gastrointestinal integrity, minimize bacterial overgrowth, and promote bile flow. In patients with extremely short gut, where complete weaning from PN is impossible, even brief periods off PN may provide some protection. Unlike continuous infusion of PN, the cyclic infusion over less than 24 hours may be beneficial because it is more physiologically similar to normal eating patterns. This strategy has been used to relieve the liver from constant exposure to high glucose and amino acid loads, although its efficacy has yet to be determined.<sup>23</sup>

Feeding beyond the liver's ability to use carbohydrate and fat can cause accumulation of by-products in the liver, resulting in hepatic injury. Although standard guidelines recommend administering lipid emulsion at a dosage less than 2.5 g/kg/d, a dosage greater than 1 g/kg/d is associated with development of PNALD.<sup>24</sup> Judicious use of intravenous fat emulsions, at a dosage of 1 g/kg/d or less, has been shown to be effective in preventing PNALD.<sup>24</sup> In the neonatal population, however, decreasing or withholding lipids for extended periods may be

detrimental owing to lack of fat reserves in preterm infants and the high risk of growth retardation.

Infections such as catheter-related sepsis can further increase the risk of PNALD.<sup>25</sup> Patients with intestinal failure are susceptible to bacterial translocation that can predispose them to sepsis. Therefore, prompt identification and treatment of suspected blood stream infections, which may require catheter removal, are imperative. The use of ethanol lock therapy to treat and prevent catheter-related sepsis is emerging as a promising new therapy.<sup>26</sup> In addition, prevention of bacterial overgrowth may also help decrease the risk of PNALD. Oral antibiotics such as metronidazole, gentamicin sulfate, and ciprofloxacin are often used as part of a treatment regimen to decrease the growth of gram-negative and anaerobic bacteria.<sup>22</sup>

There is no truly effective pharmacologic treatment of PNALD. Ursodeoxycholic acid (ie, ursodiol) has been used as an attempt to treat PNALD by improving bile flow and its solubility in order to reduce serum bilirubin and hepatic enzyme levels. The results, however, are not compelling.<sup>27</sup> Another strategy for lowering serum bile acid levels is the use of enzyme inducers such as rifampin and phenobarbital. Their results also showed limited effectiveness.<sup>28</sup> Sincalide, an investigational synthetic cholecystokin analogue, is no longer recommended.<sup>29</sup>

#### RATIONALE FOR USING PARENTERAL FISH OIL IN THE MANAGEMENT OF PNALD

Fish oil has become an emerging topic in nutrition and health care over the past several decades. Its efficacy has been widely studied in various fields, most notably cardiovascular medicine. Recently, a fish oil-based lipid emulsion, such as Omegaven (Fresenius Kabi AG, Bad Homburg, Germany), was developed for parenteral use. Unlike the soybean oil-containing Intralipid and Liposyn II, fish oil-based lipid emulsions are primarily composed of  $\omega$ -3 polyunsaturated fatty acids. However, they are currently not US Food and Drug Administration approved and are available only for compassionate use.

Fish oil-based lipid emulsions may have significant advantages over the conventional soybean oil-based lipid emulsions. Although fish oils may theoretically cause oxidative stress because they are rich in polyunsaturated fatty acids like soybean oils, lipid peroxidation products do not accumulate in liver tissue after parenteral fish oil administration. Moreover, parenteral fish oils are enriched with high levels of the antioxidant  $\alpha$ -tocopherol to counteract this possible oxidative risk.<sup>21</sup> Owing to their high concentration of  $\omega$ -3 polyunsaturated fatty acids, fish oils have anti-inflammatory potential by interfering with the proinflammatory  $\omega$ -6 pathway and producing anti-inflammatory mediators. Moreover,  $\omega$ -3 fatty acids may play a role in reducing radicals that contribute to the suppression of the inflammatory pathway.<sup>21</sup> Fish oils may modulate inflammation through the inhibition of tumor necrosis factor and by the reduction of cytokines that trigger proinflammatory reactions.<sup>21</sup>

In animal models of PNALD, parenteral fish oil administration improves biliary flow and cholestasis.<sup>30</sup> Furthermore,  $\omega$ -3 fatty acids are effective in lowering triglyceride levels in humans by increasing their clearance.<sup>30</sup> In mice,

fish oil supplementation ameliorated steatosis by reducing de novo lipogenesis and stimulation of  $\beta$ -oxidation.<sup>31</sup> Lastly, unlike soybean oil-based lipid emulsions, fish oils do not contain the hepatotoxic phytosterols that may predispose the liver to development of PNALD.

#### CLINICAL STUDIES USING PARENTERAL FISH OIL IN PNALD

To date, 8 reports have been published on the use of parenteral fish oil in the management of PNALD.<sup>5-12</sup> All studies will be discussed briefly.

The first clinical report on the use of parenteral fish oil as monotherapy, by Gura et al<sup>5</sup> in 2005, described a 16-year-old PN-dependent boy who developed EFAD due to a soy allergy. This report demonstrated the safety of fish oil monotherapy in a patient with several known risk factors (eg, bleeding, glucose intolerance), and it established that doses 5 times higher than recommended by the manufacturer and treatment for longer than 4 weeks can be safely tolerated. This report also showed that fish oil monotherapy provided enough essential fatty acids to prevent EFAD and reversed preexisting EFAD.

The 2006 case series by Gura et al<sup>6</sup> was the first to describe 2 infants with PNALD who were successfully treated with a fish oil-based lipid emulsion as demonstrated by normalization of direct bilirubin levels from greater than 2 mg/dL to normal (to convert to micromoles per liter, multiply by 17.104). This article showed that parenteral fish oil monotherapy at a dosage of 1 g/kg/d did not cause EFAD, even in a patient who received no enteral nutrition.

A 2007 case report by Gura et al<sup>7</sup> described a 12-year-old PN-dependent boy who developed EFAD when his lipid emulsion was suspended secondary to hypertriglyceridemia. Within 3 weeks of fish oil monotherapy at a dosage of 1 g/kg/d, the patient's hyperbilirubinemia reversed and he showed clinical and biochemical improvement in both EFAD and hypertriglyceridemia.

A cohort study by Gura et al<sup>8</sup> in 2008 summarized the clinical response to fish oil monotherapy in 18 infants with PNALD and compared the findings with those of a historical cohort of children who developed PNALD while being treated with the contemporary standard of care. In addition to further supporting the previously described findings, this study showed that the median time to resolution of PNALD was 9 weeks in the fish oil-treated group compared with 44 weeks in the historical cohort. Moreover, a total of 2 deaths and 0 liver transplants were recorded in the fish oil-treated cohort, whereas 7 deaths and 2 transplants were noted in the historical cohort. The mortalities in the fish oil-treated cohort were noted to be unrelated to PNALD. Gura and colleagues concluded that fish oil monotherapy at a dosage of 1 g/kg/d may be safe and efficacious in the treatment of PNALD.

A 2008 case report by Ekema et al<sup>9</sup> described the treatment of PNALD in a term infant born with midgut volvulus who required multiple operations. This patient developed cholestasis with severe hyperbilirubinemia and coagulopathy 6 months after receiving PN and the soybean oil-based lipid emulsion Lipofundin (B. Braun Melsungen AG, Melsungen, Germany) at a dosage of 3 g/kg/d. Based on the aforementioned reports, the soybean oil-

based parenteral lipid emulsion was discontinued and treatment with fish oil monotherapy was started, gradually increasing to a goal dosage of 1.5 g/kg/d. The patient's cholestasis resolved after 8 months despite continuing to receive PN.

A retrospective cohort study by Diamond et al<sup>10</sup> in 2009 reported the results of 12 infants with PNALD treated with fish oil. This study differed from all others in that children with short-bowel syndrome and severe PNALD were treated with a combination of fish oil at a dosage of 1 g/kg/d and the soybean oil–based Intralipid at a dosage of 1 g/kg/d. Four of the 12 patients showed complete resolution of their hyperbilirubinemia while receiving combination therapy. An additional 5 patients achieved complete resolution only after treatment with Intralipid was discontinued while treatment with the fish oil–based Omegaven was maintained. The remaining 3 infants went on to receive liver–small-bowel transplants. No patients developed EFAD. This report highlights the importance of using fish oil as monotherapy rather than in combination with a conventional, soybean oil–based lipid emulsion.

The 2009 case report by Calhoun and Sullivan<sup>11</sup> described an infant with midgut volvulus requiring massive small-bowel resection, resulting in short-bowel syndrome. By age 5 months, this patient developed severe PNALD while receiving Intralipid monotherapy and was listed for transplant. At that time, his parenteral lipid emulsion was switched to fish oil monotherapy at a dosage of 1 g/kg/d under a compassionate use protocol. Within 2 months, his serum bilirubin level decreased; it had returned to normal after 7 months. At the same time, the patient reached his enteral nutrition goal and was weaned from PN.

The case series by Cheung et al<sup>12</sup> in 2009 described 4 preterm infants who developed severe PNALD while receiving Intralipid at a dosage of 3 g/kg/d. The treatment was subsequently switched to parenteral fish oil monotherapy at a dosage of 1 g/kg/d. As in previous reports, Cheung and colleagues found that serum bilirubin levels began improving approximately 1 month after initiation of the fish oil–based therapy. Three of the 4 infants had complete resolution of their cholestasis while receiving fish oil. Two of them were eventually weaned off PN and were discharged home on full enteral nutrition. The 1 infant who did not improve had multiple bouts of sepsis and residual inflamed bowel resulting in ongoing intra-abdominal inflammation, multiorgan failure, and death. This case series shows that fish oil monotherapy may be efficacious in the reversal of PNALD, although some patients with ongoing complex multiorgan disease may be beyond the point of rescue.

## COMMENT

Since its first use as monotherapy in 2002,<sup>5</sup> more than 60 institutions in the United States now use intravenous fish oil to treat patients with PNALD under compassionate use protocols. Parenteral fish oils, which have anti-inflammatory effects due to their abundance of  $\omega$ -3 fatty acids, contain a higher amount of the antioxidant  $\alpha$ -tocopherol and no phytosterols. In contrast, the presence of phytosterols and proinflammatory  $\omega$ -6 fatty acids in soybean oils

may contribute to the hepatotoxic effects seen in patients receiving long-term PN with a conventional parenteral lipid emulsion. In the reviewed articles, however, there are several important differences that should be addressed. The group described by Diamond and colleagues mixes Omegaven at a dosage of 1 g/kg/d with Intralipid at a dosage of 1 g/kg/d, whereas all other groups switch the conventional lipid emulsion to fish oil monotherapy. This may explain why 5 patients who initially were receiving the combination treatment improved only when treatment with the soybean oils was discontinued. Among the groups that use parenteral fish oil as monotherapy, only the group described by Ekema and colleagues gradually increased the lipid dosage to 1.5 g/kg/d, whereas the others used a dosage of 1 g/kg/d. This lower dosage has been demonstrated to provide sufficient essential fatty acids to prevent EFAD and sustain growth. It should be emphasized that the dosage of parenteral fish oil that most investigators used is lower than the dosage they had been using for the conventional lipid emulsion. This may have been beneficial as well because it lowered the intake of total parenteral fat. Finally, it is difficult to compare patients across studies because the severity of PNALD may vary at baseline. To overcome this limitation, the efficacy and safety of the parenteral fish oil–based lipid emulsion Omegaven, compared with Intralipid, in the prevention of PNALD are currently being investigated in a randomized, controlled, double-blind clinical trial (clinicaltrials.gov identifier NCT00512629).

Although being used since the 1960s as a source of fat, soybean oil–based lipid emulsions lead to serious complications including PNALD in the PN-dependent patient. Data have emerged to show that fish oil–based lipid emulsions may be both safe and efficacious in the treatment of PNALD. Although the mechanism has yet to be fully understood, the advantages of fish oil–based lipid emulsions over soybean oil–based lipid emulsions seen to date suggest that fish oil–based lipid emulsions would be better suited for long-term PN. However, until the US Food and Drug Administration approves fish oil monotherapy in the United States, the use of parenteral fish oil–based lipid emulsions should be restricted to experienced centers for compassionate use only.

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